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Changes in Patient-Reported Symptoms After Switching From High- to Low-Sodium Oxybate in Participants With Narcolepsy in the XYLO Study

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Objective

- To examine changes in patient-reported symptoms that are associated with sodium/fluid excess after switching from high-sodium oxybate (SXB) to low-sodium oxybate (LXB)

Conclusions

- A meaningful proportion of participants with narcolepsy reported qualitative improvements in edema, diaphoresis, and nocturia after switching from SXB to LXB
  - 73% of participants reported improvement in at least 1 of these symptoms
- A limitation of this study is the small sample size, with few participants reporting severe baseline symptoms, which reduces the ability to detect potential changes
- In addition to the previously reported reduction in 24-hour ambulatory systolic BP and urine sodium excretion after participants switched from SXB to LXB, these patient-reported symptom improvements underscore broader clinical benefits of lowering sodium exposure, including relief of symptoms that may be bothersome or clinically meaningful to individuals with narcolepsy

References: 1. Ma Y, et al. *N Engl J Med.* 2022;386(3):252-263. **2.** Ben-Joseph RH, et al. *Sleep.* 2023;46(10):zsad161. **3.** Ben-Joseph RH, et al. *Mayo Clin Proc.* 2024;99(11):1710-1721. **4.** White WB, et al. *Hypertension.* 2025;82(12):2162-2171. **5.** Yoshikawa M, et al. *Neurourol Urodyn.* 2020;39(5):1550-1556. **6.** Sekii Y, et al. *Commun Biol.* 2022;5(1):175. **7.** Hoch JW, Watso JC. *Exerc Sport Sci Rev.* 2026;54(2):89-98.

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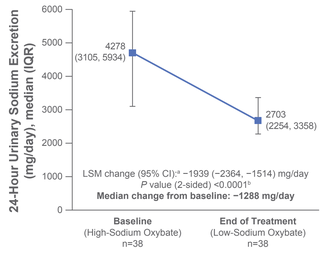
Introduction

- Excess sodium intake is associated with elevated blood pressure (BP) and a higher risk of adverse cardiovascular outcomes.[1] Because individuals with narcolepsy are at increased risk of developing hypertension and adverse cardiovascular outcomes,[2] use of high-sodium containing medications may further increase this risk[3]
- In the XYLO study (NCT05869773), participants with narcolepsy who switched from treatment with SXB to LXB reduced their daily medication-related sodium intake by a mean (SD) of 1338.8 (190.7) mg, which was paralleled by a median reduction in 24-hour urinary sodium of 1288 mg/day and clinically meaningful reductions (least squares mean change [95% CI]) in 24-hour ambulatory systolic BP of −4.1 (−6.9, −1.4) mmHg[4]

Figure 1. Reduction in Medication-Related Sodium Intake Associated With Reduction in 24-Hour Urinary Sodium Excretion and Clinically Meaningful Reductions in SBP in XYLO Participants With Narcolepsy After Switching From SXB to LXB

Medication-Related Exposure	Baseline (High-Sodium Oxybate)	End of Treatment (Low-Sodium Oxybate)
n	43	43
Dosage, mean (SD)	8.0 (1.1) g/night	8.1 (1.1) g/night
Sodium content, mean (SD)	1456.5 (206.2) mg	117.8 (16.3) mg
Difference in sodium content of medication, mean (SD)	1338.8(190.7) mg	

24-Hour Ambulatory Systolic Blood Pressure	Baseline (High-Sodium Oxybate)	End of Treatment (Low-Sodium Oxybate)
Mean (SE)	132.3 (1.8) mmHg	128.2 (1.8) mmHg
Least-squares mean change (95% CI); 1-sided *P* value	−4.1 (−6.9, −1.4) mmHg; *P*=0.0019	



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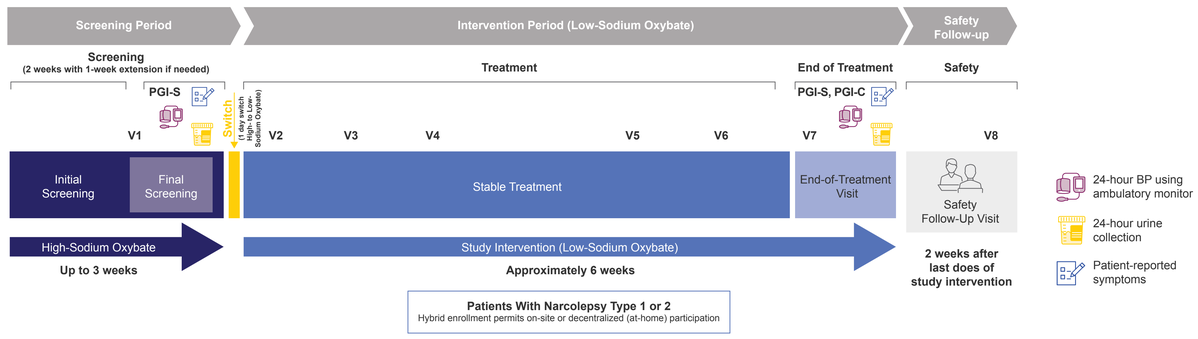
[a]Baseline-adjusted change from baseline (on high-sodium oxybate) to end of treatment (on low-sodium oxybate). [b]*P* value is nominal.
CI, confidence internal; IQR, interquartile range; LSM, least squares mean; LXB, low-sodium oxybate; SD, standard deviation; SXB, high-sodium oxybate.

- Alteration of sodium homeostasis by excess sodium intake may contribute to the development of other clinical events, such as edema,[5] nocturia,[6] and diaphoresis[7]

Methods

- XYLO was a multicenter, single-arm, open-label study in people aged 18 to 70 years with narcolepsy type 1 or 2 and office BP 130 to 155/≤95 mmHg[4]
  - Additional details on the study design can be found in the Supplement, accessed via the QR code and/or in the published article by White et al[4]
- This analysis evaluates exploratory endpoint change from baseline to end of treatment (EOT) on the Patient Global Impression of Severity (PGI-S) and change at EOT on the Patient Global Impression of Change (PGI-C) to assess the impact of switching from SXB to LXB on edema, diaphoresis, and nocturia; enuresis was not analyzed because no participants reported it at baseline

Figure 2. XYLO Study Design



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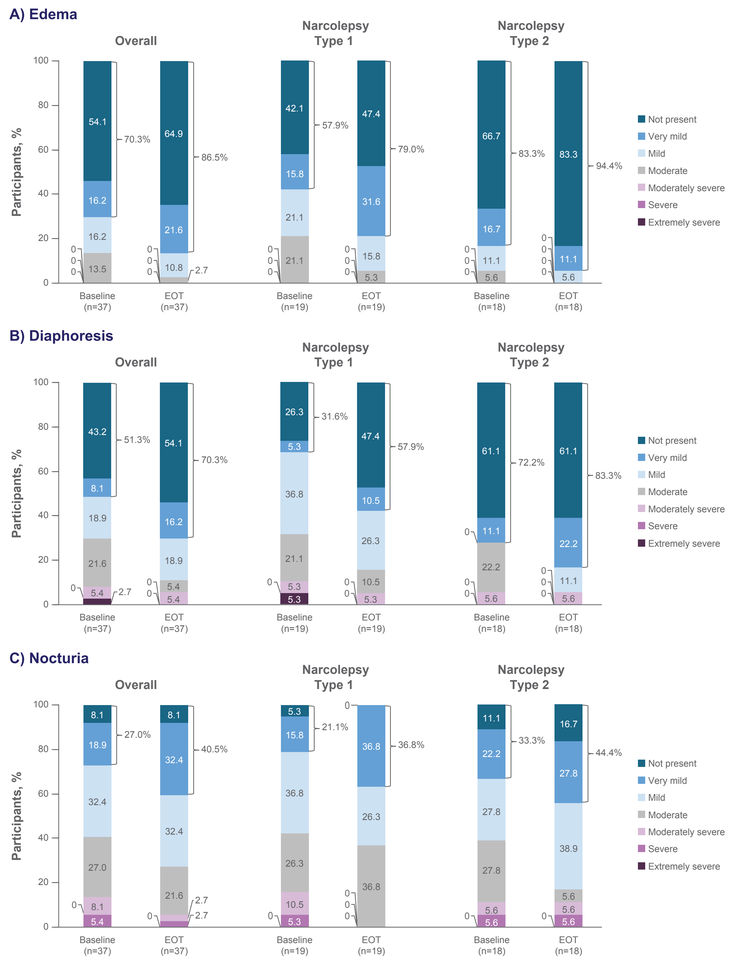
BP, blood pressure; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; V, visit.

Results

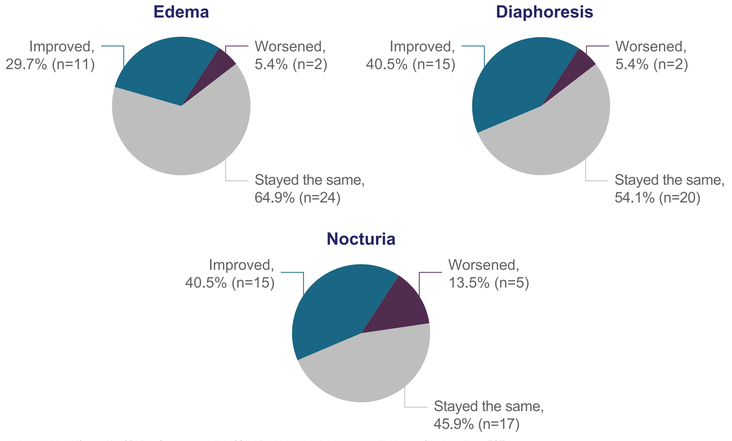
Figure 3. Proportions of Participants Reporting "Not Present" and "Very Mild" Symptoms at End of Treatment on the PGI-S Increased Relative to Baseline for A) Edema, B) Diaphoresis, C) Nocturia



EOT, end of treatment; PGI-S, Patient Global Impression of Severity.

- The proportion of participants reporting "not present" or "very mild" symptoms was lower at baseline compared with EOT for edema (difference [95% CI]: 16.2% [30.3%, 2.2%]; *P*=0.0703), diaphoresis (18.9% [33.6%, 4.2%]; *P*=0.0391), and nocturia (13.5% [24.5%, 2.5%]; *P*=0.0625) for the overall narcolepsy population

Figure 4. Most Participants Reported That the Severity of Their Symptoms Improved or Stayed the Same Rather Than Worsened at End of Treatment Relative to Baseline[a]



[a]As assessed by shift analysis of Patient Global Impression of Severity results showing any change in category from baseline to EOT.
EOT, end of treatment.

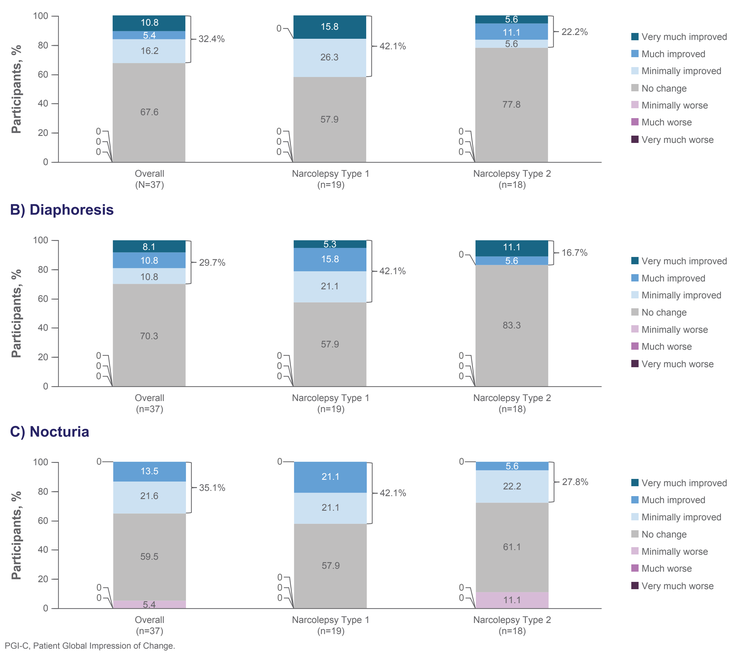
- At EOT, 27 (73%) participants improved in at least 1 symptom, with 9 (24%) participants improving in 2 or more symptoms and 6 (16%) participants improving in all 3 symptoms

Table 1. Participant Demographics and Baseline Clinical Characteristics[a]

Characteristic	NT1 (n=19)	NT2 (n=18)	Total (N=37)
Age, mean (SD), years	46.1 (11.5)	44.4 (11.9)	45.2 (11.5)
Sex at birth, n (%)			
Male	13 (68.4)	13 (72.2)	26 (70.3)
Female	6 (31.6)	5 (27.8)	11 (29.7)
Race, n (%)			
Asian	19 (100)	1 (5.6)	1 (2.7)
Black or African American		1 (5.6)	1 (2.7)
White		2 (11.1)	2 (5.4)
Unknown		14 (77.8)	33 (89.2)
BMI, kg/m², mean (SD)	30.3 (6.9)	28.9 (9.0)	29.6 (7.9)
Office seated BP, mmHg, mean (SD)			
Systolic	139.4 (5.3)	136.8 (6.5)	138.2 (6.0)
Diastolic	86.3 (6.3)	83.2 (6.7)	84.8 (6.6)
Concomitant medications, n (%)			
Antihypertensives[b]	7 (36.8)	6 (33.3)	13 (35.1)
Alerting agents	16 (84.2)	14 (77.8)	30 (81.1)
Total baseline high-sodium oxybate dosage, g/night; mean (SD)	8.1 (1.2)	8.2 (1.0)	8.2 (1.1)
Relevant comorbidities, n (%)			
Sleep apnea	5 (26.3)	5 (27.8)	10 (27.0)
Dyslipidemia	4 (21.1)	4 (22.2)	8 (21.6)
Obesity	5 (26.3)	1 (5.6)	6 (16.2)
Diabetes	1 (5.3)	1 (5.6)	2 (5.4)

[a]Subset of the 43 IA participants who completed the 6-week EOT visit, had a qualifying 24-hour BP recording, and had both baseline and EOT PGI-S data. [b]The specific antihypertensives and proportion of participants on 1 or multiple antihypertensive(s) can be found in the Supplement, accessed via the QR code.
BMI, body mass index; BP, blood pressure; EOT, end of treatment; IA, interim analysis; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

Figure 5. Approximately One-Third of Participants Reported Improvement in Edema, Diaphoresis, and Nocturia at End of Treatment on the PGI-C



PGI-C, Patient Global Impression of Change.

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Supplemental Methods

Supplemental Figure S1. Key Enrollment Eligibility Criteria

Inclusion Criteria

- 18–70 years of age with documented diagnosis of narcolepsy type 1 or 2
- Taking **twice-nightly SXB 6–9 g/night for ≥6 weeks** before screening
- Patients using antihypertensives, stimulants, and/or alerting agents or other medications known to affect BP at study entry were required remain at the same doses throughout the study unless advised otherwise due to safety concerns
- Average screening office SBP (3 measures at 1-minute intervals) between **130–155 mmHg (inclusive)**
- Average screening office DBP (3 measures at 1-minute intervals) **≤95 mmHg**

Exclusion Criteria

- History of treatment-resistant hypertension[a]
- History or presence of an acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect participant safety or interfere with study assessments or participation
- Presence of significant cardiovascular disease, atrial fibrillation, or renal impairment (estimated glomerular filtration rate <45 mL/min)
- Occupation requiring nighttime or variable shift work

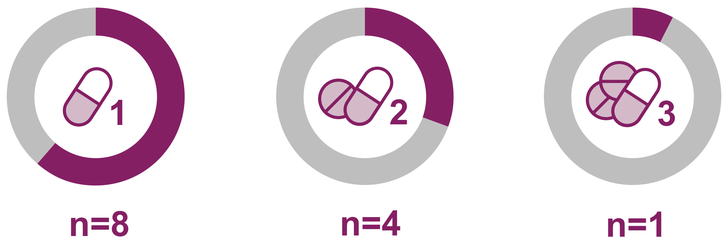
Dietary salt was not monitored or restricted; participants were asked to maintain consistent sleeping and dietary habits and exercise regimens. [a]Defined as requiring ≥4 antihypertensive medications for BP control or uncontrolled BP with 3 or more antihypertensive medications of different classes that include a diuretic.
BP, blood pressure; DBP, diastolic blood pressure; min, minute; SBP, systolic blood pressure; SXB, high-sodium oxybate.

Supplemental Results

Supplemental Table S1. Use of Antihypertensive Medications in ≥1 Participant (n=13/37 [35.1%])

Medication, n (%)	Total (N=37)
Participants taking concomitant antihypertensives	13 (35.1)
Lisinopril	4 (10.8)
Metoprolol	4 (10.8)
Amlodipine	2 (5.4)
Hydrochlorothiazide	2 (5.4)
Losartan	2 (5.4)
Benicar (Olmesartan)	1 (2.7)
Spironolactone	1 (2.7)
Toprol	1 (2.7)
Verapamil	1 (2.7)
Zestoretic	1 (2.7)

Supplemental Figure S2. Number of Antihypertensive Medications Used at Baseline Among Those Taking Antihypertensive Medications at Baseline



- Of the 13 (35.1% of the analysis population) participants taking antihypertensives at baseline, 8 (61.5%), 4 (30.8%), and 1 (7.7%) were taking 1, 2, and 3 antihypertensives, respectively

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